Remarks

The Examiner has rejected all pending claims (claims 1-15) for obviousness over Bollag *et al.*, and provisionally rejected all claims for obviousness-type double patenting over U.S.S.N. 09/874,514, now issued as U.S. Patent 6,849,651.

In order to further prosecution, Applicant has canceled claims 1-15 and added new claims 16-29 which recite compositions and methods of use comprising an "epothilone macrolide" at a particular dosage range and a pharmaceutical carrier selected from the group consisting of "glycols, oils, and alcohols." These amendments should not be taken as a disclaimer of any subject matter; Applicant explicitly reserves the right to pursue subject matter that was pending prior to this amendment in future applications. Although the cancellation of claims 1-15 renders the outstanding rejections moot, Applicant has addressed below each of the rejection as they apply to the new claims.

I. Support for Claim Amendments

As discussed in the interview in regard to USSN 09/874,514, now issued as U.S. Patent 6,849,651, the present specification describes a variety of studies in which compositions comprising epothilone B were administered to mice in order to study both its toxicity and its efficacy. The *lowest* dose at which severe toxicity was observed was 0.6 mg/kg (see, for example, Figure 47 and Table 11 [all mice receiving 0.6 mg/kg died], as well as Figure 44B and Table 12 [5/8 mice receiving 0.8 mg/kg died, but only 1/8 mouse receiving 0.4 mg/kg died]); this dose is recited as the upper maximum in the present claims.

The data presented in the specification also demonstrate successful inhibition of tumors with regimens in which individual doses are interrupted by at least one (see, for example, Table 13; recited in claim 132) or three (see, for example, Table 8; recited in claim 133) days of rest; introducing such interruptions into the administration schedule reduced the average daily dose in almost every case to below 0.6 mg/kg, as is recited in the present claims (for example claim 129).

The data presented in the specification also demonstrate successful inhibition of multidrug-resistant tumors (see, for example, Table 8; recited in claim recited in claim 135), and

show at least about 16% tumor inhibition (see, for example, Tables 8 and 13; recited in claim 136).

The present specification also describes compositions and methods using analogues of epothilones, particularly analogues related to epothilone B, supporting use of the term "epothilone macrolide" in the claims (see lines 12-27 on page 33). The specification also describes compositions formulated for a variety of different delivery routes including parenteral (recited in claim 125) and oral (recited in claim 126) (see, for example, page 34). The specification specifically mentions glycols, oils, and alcohols are desirable pharmaceutical components (see, for example, page 34, line 16).

Thus, the present claims, as amended, are fully supported by the specification as filed. No new matter is added to the case by the present Amendments.

II. Nonobviousness over Bollag *et al.*

As noted above, the Office Action rejected all pending claims as obvious in light of Bollag *et al.* The Office Action states that "Bollag et al., teach . . . epothilones A . . . and B . . . and methods of use for treating cancer or tumor . . . " (page 3), and further states that "claiming variable effective amounts of the epothilones . . . is not in and of itself patentable over the prior art of Bollag et al." Applicant strongly disagrees.

First, Applicant points out that Bollag *et al.* do not teach methods of using epothilones A and B to treat *cancer* or *a tumor*, as stated by the Examiner. Bollag *et al.* teach the use of a compound purified from *Sorangium cellulosum* to kill isolated cells *in vitro*. Bollag *et al.* do not rigorously demonstrate that the compounds they isolated are epothilones A and B, they merely report that their spectral analyses "suggest" that their compounds are the same as epothilones A and B described by someone else (see page 2327). *Sorangium cellulosum* are known to produce a variety of epothilone compounds and isomers; it is conceivable that the compounds that Bollag *et al.* tested were not epothilones A and B at all. *See* Hardt *et al., J. Natl. Prod.* 64(7):847-856 (July 2001).

Even if the compounds that Bollag *et al.* tested were epothilones A and B, Bollag *et al.* provide no teaching or suggestion that the compound can *treat cancer* or *kill tumors*. The mere demonstration that a compound can kill cells *in vitro* cannot render obvious the present claims to

compositions reciting particular amounts of that compound that are effective at treating cancer or inhibiting tumors *in vivo*. As Applicant has previously argued, Bollag *et al.* at most provided an invitation to experiment, to *try to identify* an amount of the compound that could be useful in treating cancer or inhibiting tumor growth. There was no reasonable expectation, based merely on the teachings of Bollag *et al.*, that such an amount could be identified.

In fact, as Applicant has previously indicated and has been discussed in both in-person and telephonic interviews, epothilone B shows unexpectedly severe toxicity. The data presented in the present specification attest to the challenges associated with defining a therapeutic index for epothilone B. The present specification establishes that doses of epothilone B above 0.6 mg/kg often result in unacceptable toxicity (see, for example, Figure 47 and Table 11; see also Figure 44B and Table 12). In one experiment, *all* mice receiving this dose died!

For all of these reasons, Applicant respectfully submits that the teachings of Bollag *et al.* cannot render obvious the present claims; the rejection can be removed.

III. Double Patenting

In the Office Action, all claims were provisionally rejected for statutory double patenting over claims 148, 150, 154, and 161-171 of USSN 09/874,514 and claims 123-136 of USSN 10/058,695. Applicant respectfully refrains from commenting on these rejections unless and until such time as they mature into actual rejections.

In light of the foregoing Amendments and Remarks, Applicant respectfully submits that the present application is in condition for allowance; a Notice to that effect is respectfully requested.

If it is believed that a telephone conversation would expedite matters, the Examiner is invited to contact the undersigned at (617) 248-5215. The Examiner is authorized to charge any fees associated with this amendment, or to refund for any overpayment, to our Deposit Account No.: 03-1721.

Respectfully submitted,

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